

REMARKS**I. Status of Claims**

Claims 61-91, 95 and 97 have been withdrawn.

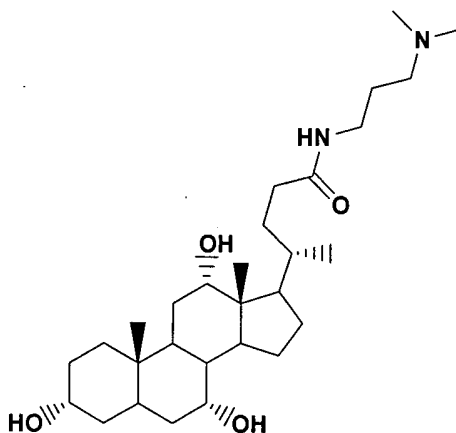
Claim 96 is pending and has been examined.

Claim 96 stands rejected as obvious over US 4,372,888 ("the '888 Patent") in view of *Hjelmeland, Proc. Natl. Acad. Sci. U.S.A.* 77(11):6368-70 (1980) ("*Hjelmeland*").

Claim 96 has been amended. Support for the amendments to claim 96 is found throughout the specification as filed, for example on page 11, lines 1-6 and 8-14.

II. Response to Claim Objections

The Patent Office objected to claim 96 and requested clarification of the structure and IUPAC name of mCHAPSO. Applicants provide herewith the IUPAC name and structure of mCHAPSO:



N-[3(dimethylamino)propyl] 3, 7, 12-trihydroxy(3a, 5b, 7a, 12a)cholan-24-amide

Applicants have amended claim 96 to be consistent with the above-presented name and structure and regret any confusion.

III. Response to the Rejection of Claim 96 Under 35 U.S.C. §103(a)

The Patent Office rejected claim 96 under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 4,372,888 ("the '888 Patent") and *Hjelmeland*, (1980) *Proc. Natl. Acad. Sci. U.S.A.* 77(11): 6368-6370 ("*Hjelmeland et al.*"). The Patent office characterizes the '888 patent by stating that

“the structure of mCHAPSO is contemplated by US ‘888 as it is displayed as a ‘positive hit’ in the structure search of the compound along with the abstract of US ‘888, therefore being, in essence, ‘taught.’” *Office Action*, page 4. The Patent Office states that it would have been obvious to one of ordinary skill in the art “to make ‘mCHAPSO’ by combining the cholic acid with the $R-(CH_3)_2-NH_2$ functional group as taught by US ‘888 and to use it to purify membrane proteins.” *Office Action*, page 5. The Patent Office further states that “a person of ordinary skill in the art would have been motivated to make mCHAPSO and use it because Hjelmeland teaches that ionic detergents are better than nonionic detergents to isolated integral membrane proteins.” *Office Action*, page 5. Finally, the Patent Office states that “a person of ordinary skill in the art at the time of the invention was made would have a reasonable expectation of success because both cholic acid (the starting material), CHAPSO, CHAPS, and several operative compounds (the products) as taught by US ‘888 work for this process. Since mCHAPSO is an intermediate between cholic acid and CHAPSO, it shares the key core structures of cholic acid and a polar side group, which bestow upon it detergent properties. A person of ordinary skill in the art at the time of the invention would have a reasonable expectation of its activity because of it belonging to this class of compounds which share the key structures and all share the same function as detergents.” *Office Action*, page 5. Applicants traverse the rejection and submit the following comments.

III.A. The Patent Office Did Not Present a Prima Facie Case of Obviousness

The Patent Office rejected the pending claims under 35 U.S.C. §103(a) over a single combination of references. Before specifically addressing the rejections, applicant notes that in *Graham v. John Deere Co.* the U.S. Supreme Court set forth the factual determinations to be made, as well as the evidence to consider, in making an obviousness determination under §103 as including:

- (a) the scope and content of the prior art;
- (b) the differences between the prior art and the claimed subject matter as a whole;
- (c) the level of ordinary skill in the pertinent art; and
- (d) where relevant, additional objective evidence, which may serve as indicia of non-obviousness.

Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). See also *Environmental Design Ltd. v. Union Oil Co.*, 713 F.2d 693, 695 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984). All relevant evidence on each of these four dispositive issues must be fully considered and evaluated to determine whether the claimed invention would have been obvious. *Ibid.* The first three of these factual determinations comprise the *prima facie* case of obviousness. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000).

Applicant also notes the “tenets of patent law that must be adhered to when applying §103” as outlined by the Court of Appeals for the Federal Circuit: the claimed invention must be considered as a whole; the references must be considered as a whole and suggest the desirability and thus the obviousness of making the combination; the references must be viewed without the benefit of hindsight vision afforded by the claimed invention. *Hodosh v. Block Drug Co.*, 786 F.2d 1136, 1143, n.5 (Fed. Cir. 1986) (citations omitted). The *Hodosh* court also noted that “ought to be tried” is not the standard with which obviousness is determined. *Ibid.*

Additionally, it is well known that a *prima facie* case of obviousness requires that in addition to the requirement that the cited document or combination must disclose all aspects of the claimed invention (*Graham* at 17-18), the combination must contain a suggestion to modify the cited document(s) to arrive at the claimed invention (see, e.g., *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (citing *In re Rouffet*, 149 F.3d 1350, 1357-58 (Fed. Cir. 1988)), and there must be a reasonable expectation of successfully reaching the claimed invention as a result of the modifications (*Boehringer Ingelheim Vedmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003)).

Finally, applicant notes the Court of Appeals for the Federal Circuit’s admonition in *Jones v. Hardy*: “The test under §103 is not whether an improvement or a use set forth in a patent would have been obvious or nonobvious. The test is whether the claimed invention, considered as a whole, would have been obvious or nonobvious.” *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984).

Bearing the above in mind, applicant traverses the various obviousness rejections and addresses each asserted combination in turn. Summarily, applicant submits that when the claimed invention is considered *in toto* and in view of the cited references, alone or in combination, the claimed invention is not obvious and represents a significant and patentable advance in the field.

The Cited Combination Fails the First Prong of the Obviousness Inquiry Because it Does Not Disclose Each and Every Element of the Claimed Invention

Applicants have amended claim 96 to recite the isolation of a gamma secretase or a gamma secretase complex using mCHAPSO. Neither the '888 Patent nor *Hjelmeland et al.*, which appears to generally parallel the disclosure of the '888 Patent, teaches the isolation of a gamma secretase protein or protein complex using mCHAPSO.

Applicants further submit that neither Hjelmeland nor the '888 patent teaches the synthesis or structure of mCHAPSO. The '888 Patent apparently teaches the synthesis of CHAPS and CHAPSO, but applicants note that the '888 Patent does not teach the synthesis or structure of mCHAPSO in any form. Applicants respectfully submit that the appearance the '888 Patent abstract in the Patent Office's structure search of mCHAPSO does not qualify the '888 Patent as a reference teaching the synthesis or structure of mCHAPSO.

Applicants submit that the proposed combination does not render claim 96 obvious, because the cited references do not teach each and every element of the claimed invention. The proposed combination, therefore, fails the first prong of the *prima facie* case of obviousness.

The Cited Combination Fails the Second Prong of the Obviousness Inquiry Because it Does Not Provide the Requisite Motivation

Applicants note that the invention must be considered as a whole, and not as the sum of its parts. As the Federal Circuit recently stated, "The 'as a whole' instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might successfully break an invention into its component parts, then find a prior art reference corresponding to each component. This line of reasoning would import hindsight into the obviousness determination by using the invention as a roadmap to find its prior art components. Further, this improper method would discount the value of combining various existing features or principles in a new way to achieve a new result—often the essence of invention." *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1337 (Fed. Cir. 2005) (citations omitted).

As the '888 Patent states, "One of the more important aspects of the purification of membrane proteins is the choice of a suitable detergent." '888 Patent, col. 2, lines 12-14. This sentiment is also stated in *Hjelmeland et al.* (*Hjelmeland et al.*, page 6368, first sentence).

Taking the teachings of the cited references as a whole, applicants submit that one of ordinary skill in the art would look no further than CHAPS or CHAPSO, the properties of which are extolled by the cited references, to identify a detergent for purifying a membrane protein or protein complex. There is no suggestion or motivation provided by the cited references to backtrack through the synthesis of CHAPS or CHAPSO to find mCHAPSO. Applicants submit that one of ordinary skill in the art would recognize the apparent increase in solubility provided by CHAPSO over CHAPS and other detergents ('888 *Patent*, Figure 2 and col. 9, line 67 through col. 10, line 2) and look no further for a suitable detergent. With the complete synthesis of CHAPSO apparently provided in the '888 *Patent*, coupled with the discussion and presentation of the presumed advantages of CHAPSO over CHAPS, there would be no reason for one of ordinary skill in the art to look further, and moreover not to consider intermediates in the preparation of these detergents.

Moreover, applicants submit that although CHAPSO may be suitable for solubilizing opiate receptors ('888 *Patent*, col. 9, line 67 through col. 10, line 2), this does not necessarily mean that it is optimal for solubilizing gamma secretase, an element recited in claim 96. In other words, the observation that CHAPSO is effective to solubilize opiate receptors would not provide the requisite motivation to deconstruct the synthetic pathway for CHAPSO to identify mCHAPSO as a particularly effective detergent for solubilizing gamma secretase.

Applicants further submit that mCHAPSO is an intermediate in the synthesis of CHAPSO and, as such, there would be no motivation whatsoever for one of ordinary skill in the art to consider a CHAPS or CHAPSO intermediate as a detergent when the properties of CHAPS and CHAPSO themselves are discussed in the cited references. Restated, when presented with the complete synthesis of CHAPSO, one of ordinary skill in the art would not be motivated to consider the utility of an intermediate for the purification of gamma secretase.

Lastly, applicants note that the surfactant and micellar properties of CHAPS and CHAPSO would be expected to result from the combination of the hydrophobic portion (tail) of the molecule (the cholic residue) with the polar head (the zwitterionic portion, or internal or inner salt) resulting from the quaternary nitrogen and the sulfonic acid moiety. mCHAPSO lacks such a polar head. More particularly, there is no ionic species present in the molecule. Since no internal or inner salt or zwitterion is present in mCHAPSO, one of ordinary skill in the art would not expect mCHAPSO to serve as a micellar complex or surfactant that would be useful or

desirable for use in the isolation of a gamma secretase protein or gamma secretase complex. Summarily, one of ordinary skill in the art would not be motivated to employ mCHAPSO in the isolation of a gamma secretase protein or protein complex, because unlike the chemistry of CHAPS and CHAPSO, the chemistry of mCHAPSO does not suggest that it would be useful, or more useful than CHAPS or CHAPSO, for isolating a gamma secretase protein or protein complex.

Applicants submit that the proposed combination does not render claim 96 obvious, because the cited references do not provide the requisite motivation to make the proposed combination. The proposed combination, therefore, fails the second prong of the *prima facie* case of obviousness.

The Cited Combination Fails the Third Prong of the Obviousness Inquiry Because it Does Not Provide a Reasonable Expectation of Success

As noted above, there is a high degree of variability in the behavior of a given detergent to solubilize a given protein or protein complex, and even relatively small structural differences can provide significant differences in solubilization ability. As the '888 Patent points out, the relatively minor structural differences between CHAPS and CHAPSO lead to a roughly two-fold difference in the solubilization of opiate receptors ('888 Patent, col. 9, line 67 through col. 10, line 2). Accordingly, applicants submit that the Patent Office's belief that "[a] person of ordinary skill in the art at the time of the invention would have a reasonable expectation of its [mCHAPSO's] activity because of it belonging to this class of compounds which share the key structures and all share the same function as detergents" (*Office Action*, page 5) is not tenable. Although cholic acid, CHAPSO and mCHAPSO may all share key structures, the variability between CHAPS and CHAPSO, coupled with the difference in the ability to solubilize a protein or protein complex, as evidenced by Example 2 of the '888 Patent, indicates that simply having similar key structures does not guarantee success in solubilizing gamma secretase.

Applicants submit that the proposed combination does not render claim 96 obvious, because the proposed combination does not provide a reasonable expectation of success. The proposed combination, therefore, fails the third prong of the *prima facie* case of obviousness.

IV. Conclusion

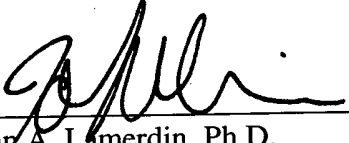
In view of the amendments and remarks, applicants respectfully request that the objections and rejections of record be reconsidered and withdrawn. Applicants further submit that the subject patent application is in condition for allowance.

Although it is believed no additional fee is due, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment associated with the filing of the instant Response to Deposit Account Number 19-3880. Furthermore, if any extension of time not already accounted for is required in connection with the filing of the instant Response, such extension is hereby requested.

If any small matter should remain outstanding after the Examiner has had an opportunity to consider the instant Amendment and Response, the Examiner is respectfully requested to telephone the undersigned attorney in order to expeditiously resolve these matters.

Respectfully submitted,

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Date: September 9, 2005